PSJ2 Exh 27

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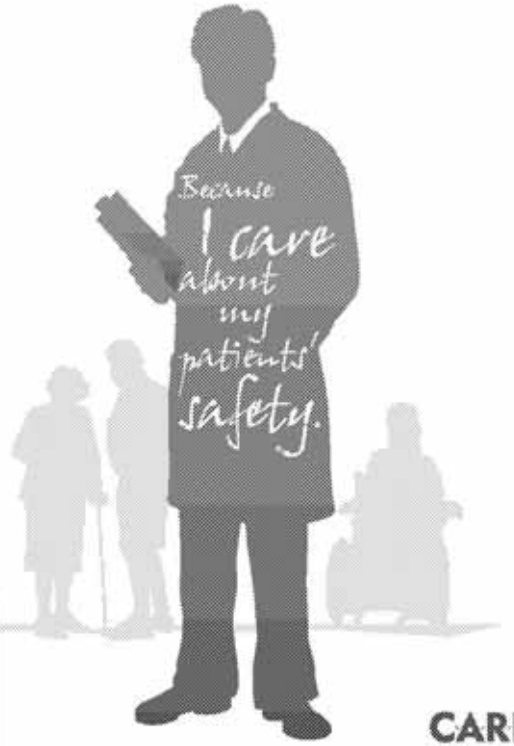
Opioid Clinical Management Guide

A Resource for Responsible Opioid Prescribing and Use



CARESAlliance
Collaborating & Acting Responsibly to Ensure Safety

The C.A.R.E.S. Alliance

The C.A.R.E.S. Alliance is committed to providing education and resources to health care professionals (HCPs) and patients about medication risks, responsible prescribing, and safe use.

Safe and effective therapy for the management of chronic noncancer pain requires clinical skills and knowledge of the principles of good opioid prescribing and the assessment and management of risks associated with opioids.[1]

These risks include:

- **Misuse**—use of a medication prescribed for a legitimate medical purpose other than as directed or indicated[2]
- **Abuse**—use of a medication for a nonmedical purpose such as altering one's state of consciousness (ie, getting high)[2]
- **Addiction**—a neurobiologic disease characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving[3]
- **Overdose**—use of larger quantities of an opioid medication than can be physically tolerated, resulting in serious and sometimes fatal toxic reactions, including central nervous system (CNS) and respiratory depression. Opioid overdose can be manifested by respiratory depression and extreme somnolence[4, 5, 6, 7] (see Glossary of Terms, p. 33 for a more complete definition).
- **Diversion**—the intentional transfer of a controlled substance from legitimate distribution and dispensing channels[2]

This Clinical Management Guide summarizes years of experience by leading pain management and addiction medicine specialists and guidance from leading health care organizations.

The information provided in this guide should help you optimize the effectiveness of opioid analgesics and thereby improve patient outcomes in your clinical practice by

- Understanding the risks and potential adverse events associated with opioids
- Performing careful patient evaluation and structuring of opioid therapy to accommodate increased risk
- Appropriately initiating and titrating chronic opioid therapy
- Counseling patients on the risks and benefits of opioid therapy as well as on safe use and handling, including proper disposal
- Performing regular and comprehensive patient monitoring

Guideline Spotlight

Throughout this document the American Pain Society and American Academy of Pain Medicine (APS/AAPM) Clinical Guidelines are highlighted for the reader

Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.

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Introduction

The use of opioid analgesics for the treatment of chronic noncancer pain has increased steadily since 1980.[8,9] Opioids are now recognized as effective therapy for select patients when prescribed judiciously and appropriately by health care professionals (HCPs) who are knowledgeable about and skilled in assessing and managing the potential associated risks, including misuse, abuse, addiction, overdose, and diversion.[2] HCPs will encounter these risks in clinical practice when they prescribe opioids for their patients with chronic noncancer pain.

Optimizing the effectiveness of opioid analgesics in clinical practice requires HCPs to

- Properly select patients for opioid therapy by evaluating the benefits and risks[2]
- Stratify patients according to their individual risk profile for opioid misuse, abuse, and addiction[2]
- Counsel patients on the potential benefits and risks of opioid therapy[2]
- Gain informed patient consent to opioid therapy with full knowledge of treatment goals, expectations, potential risks, and treatment alternatives[2]
- Define HCP and patient responsibilities and expectations using a written opioid use agreement[2]
- Monitor patients periodically and as warranted, including the use of urine drug screening (UDS) to confirm adherence to the prescribed opioid treatment plan[2]
- Manage patients who are at high risk for or who are currently engaging in aberrant drug-related behaviors[2]
- Collaborate with or refer patients to specialists such as mental health or addiction specialists when needed[2]

Misuse and Abuse in Patients With Pain

Patients have a right to proper, respectful, informed, and nondiscriminatory pain management and care.[10] However, all patients treated with opioids should be carefully monitored for signs of abuse and addiction. HCPs should also be aware that abuse of prescription opioids comes primarily through legitimate prescriptions from a single prescriber. Prescription opioids may be misused or abused by the patients to whom they are prescribed for legitimate medical purposes and by others who obtain them from these patients.[11]

Nearly 1 in 5 patients (18%) who abuses prescription opioids obtains them from a legitimate prescription from a single doctor.[11] Furthermore, estimates of primary care patients with pain engaging in aberrant behaviors or with urine drug screens positive for illicit substances such as cocaine or marijuana range from 10% to 40%.[12]

Risk Factors for Abuse

HCPs should be aware of and screen for individual risk factors for abuse, including:

- Personal or family history of substance abuse[14]
- History of preadolescent sexual abuse[14]
- Mental disease / pathology[14]
- Social patterns of drug use[14]
- Psychological stress[13]

The primary risk factor for misuse is uncontrolled or inadequately treated pain.[15]

Why Patients Misuse or Abuse Prescription Opioids

Patients with pain who abuse prescription opioids identify the following reasons for their misuse or abuse.[13] These reasons can provide a roadmap for HCPs to proactively intervene with patient counseling and education.

- Uncontrolled pain / pseudoaddiction (drug-seeking behavior as a result of undertreatment)
- Rational misuse (intentional misuse to improve function and quality of life)
- Chemical coping (intentional misuse as a result of stress or mental disease)
- Psychosocial or emotional issues
- Psychiatric disorders
- Addiction
- Recreational use and / or use with other prescription or illicit drugs

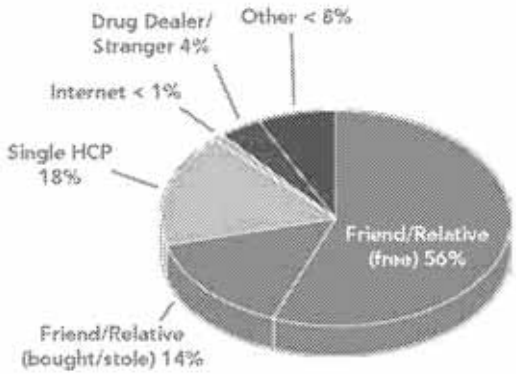
HCPs Can Reduce the Risk of Misuse and Abuse By

- Screening patients for risk of misuse, abuse, and addiction
- Stratifying treatment for risk of misuse, abuse, and addiction
- Regularly monitoring patients for changes in potential risk factors, including aberrant drug-related behaviors and results of urine drug screening
- Encouraging patients to read the FDA approved Medication Guide and / or other patient information that accompanies the product
- Counseling patients on safe use, handling, and storage

Abuse of Prescription Opioids by Non-Patients

More than two-thirds (70%) of individuals who abuse prescription opioids obtain them from a friend or relative (Figure 1).[11] Among those who abuse prescription opioids, 88% obtain them from a friend, relative, or from a single HCP.[7]

Figure 1: Sources of Prescription Opioid Abuse



HCPs who prescribe opioid analgesics can unwittingly be at the head of the supply chain for opioid abuse and, therefore, have an opportunity to break the chain by

- Screening patients for risk of abuse, addiction, and diversion
- Stratifying treatment for risk of abuse and addiction
- Regularly monitoring patients for changes in risk factors for abuse, addiction, and diversion, including aberrant drug-related behaviors and urine drug screening
- Counseling patients on the risks to family, friends, and household acquaintances of opioid abuse and overdose, as well as on the importance of keeping prescription opioids secure against theft and accidental use[2]

Addiction

Opioids prescribed for the treatment of chronic pain are Schedule II controlled substances that can be abused. Use of opioid analgesics carries the risk of addiction even under appropriate medical use.[2,4,5,6,16]

Addiction is a primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations.[15] Addiction is characterized by behaviors that include one or more of the following[15]:

- Impaired control over drug use
- Compulsive use
- Continued use despite harm
- Craving

Concern about addiction can be an impediment to opioid prescribing and use, resulting in undertreatment of pain, inadequate pain relief, unnecessary suffering, and increased health care costs.[3] However, a study of patients with chronic pain who were treated with opioid analgesics in the primary care setting found that the rate of opioid use disorders was 4-fold higher than in the general population (3.8% vs 0.9%).[17]

Before prescribing opioid analgesics for chronic pain, HCPs should perform a thorough history, physical examination and appropriate testing, and assess the patient's risk for addiction.[2] (See Risk Stratification, p. 13.)

Pseudoaddiction

Some patients may exhibit aberrant behaviors, including inappropriate drug seeking behaviors when pain is undertreated. Unlike true addiction, however, these behaviors resolve and function and quality of life increase when pain is effectively treated.[15]

Overdose

Respiratory depression is a chief hazard of opioids and may occur in patients who are not opioid tolerant or who take an opioid at too high of a dose.[2, 4, 5, 6, 7, 16] In fact, Schedule II opioids, including hydromorphone, morphine, oxycodone, fentanyl, oxymorphone, and methadone, have the highest potential risk of fatal overdose due to respiratory depression.[7]

Overdose may occur by

- Altering the recommended administration of opioid analgesics, such as by breaking, chewing, dissolving, or crushing tablets; by snorting, injecting, or inhaling ingredients meant to be swallowed whole; or by taking a transdermal opioid orally.[4, 5, 6, 7, 16] These may lead to rapid release and absorption of a potentially fatal opioid dose.[4, 5, 6, 7, 16] This is especially true for extended-release opioids
- Accidental consumption by children[4, 5, 6, 7, 16]
- Use by anyone for whom they were not prescribed
- Use of doses greater than 60 mg morphine equivalents in patients who are not opioid tolerant[4, 16]
- Overestimating the dose when converting a patient's dose from another opioid medication[7, 16]
- Titrating a patient too quickly to allow sufficient time for blood levels to reach steady state (especially when converting to methadone from other opioid analgesics)
  - Taking opioids concomitantly with alcohol[4, 5, 6, 7, 16]
  - Taking opioids with other CNS depressants[4, 5, 6, 7, 16]
- Use in patients
  - With impaired respiratory function[4, 5, 6, 7, 16]
  - With debilitated health[4, 5, 6, 7, 16]
  - Who do not take opioids exactly as directed[4, 5, 6, 7, 16]
  - Who misuse or abuse opioids[4, 5, 6, 7, 16]
  - Who take opioids concomitantly with alcohol[4, 5, 6, 7, 16]
  - Who take opioids with other CNS depressants[4, 5, 6, 7, 16]

Adverse Events

Certain adverse events are commonly associated with opioid therapy and can, therefore, be anticipated and either treated prophylactically or managed if they occur. The most common adverse events associated with oral opioid analgesics occurring in >10% of patients are generally gastrointestinal or central nervous system related and include:

- Constipation[2, 4, 6, 7]
- Nausea[2, 4, 5, 6, 7]
- Vomiting[6, 7]
- Somnolence[2, 4, 6, 7]
- Headache[7]
- Asthenia, including fatigue[7]
- Dizziness[6, 7]
- Pyrexia[5]
- Pruritis[6]

Guideline Spotlight

- HCPs should anticipate, identify, and treat common opioid-associated adverse events[2]

In addition to understanding these risks, HCPs should ensure that patients understand them and know how to use the medication safely. (See Patient Counseling, p. 21.)

Selecting Appropriate Patients for Opioid Therapy

Proper patient selection is integral to responsible opioid prescribing and use.[2] HCPs should make a diagnosis with appropriate differential,[17] including the components of an effective patient evaluation presented below. HCPs should individualize treatment for every patient using nonopioid analgesics, opioids as needed and/or combination analgesics, or chronic opioid therapy in a progressive plan of pain management (Figure 2) in keeping with the World Health Organization and the Federation of State Medical Boards guidelines.[4,5,7,18]

Figure 2: World Health Organization 3-Step Analgesic Ladder[19]

Adapted from: World Health Organization. *Cancer pain relief: with a guide to opioid availability.* 2nd ed. Geneva, Switzerland: World Health Organization; 1996.

Guideline Spotlight

- HCPs may consider a trial of opioid therapy in patients whose pain is moderate to severe, and is having an adverse impact on function or quality of life, and in whom the potential therapeutic benefits outweigh the potential harms[2]

Before initiating treatment, HCPs must conduct, and document in the medical record, an effective patient evaluation, including assessment of risk of substance misuse, abuse, addiction, and overdose.[2,18]

Components of an Effective Patient Evaluation

- Conduct a comprehensive physical examination, including appropriate diagnostic testing[2]
- Characterize the pain and assess its impact on the patient's ability to function and quality of life[1]
- Conduct appropriate diagnostic tests to assess the underlying pain condition and determine the suitability of treatment with nonopioid therapy[2]
- Conduct a thorough patient history, including assessment of psychosocial factors and family history, to aid in risk stratification[2]
- Assess risk of abuse and addiction using patient and family history of substance abuse and validated risk assessment tools such as[2]
  - Opioid Risk Tool (ORT)
  - Screener and Opioid Assessment for Patients with Pain (SOAPP) v1.0 and the revised SOAPP (SOAPP-R)
- Conduct a comprehensive benefit-to-harm analysis to determine the appropriateness of opioid therapy[2]

Structuring Therapy According to Risk (Risk Stratification)

After performing an effective patient evaluation, HCPs should structure opioid therapy to accommodate the identified risk.[2] Figure 3, below, presents a proposed method for stratifying patients into basic groups according to lower, moderate, and higher risk. This can be used as a practical framework to help determine which patients may be safely treated in the primary care setting, those who should be co-treated with specialist support, and those who should be referred on for management of their chronic pain condition in a specialist setting.

Figure 3: Risk Stratification

Lower Risk	Moderate Risk	Higher Risk
Primary Care Patients	Primary Care Patients With Specialist Support	Pain Specialist Patients
ORT Score: 0-3	ORT Score: 4-7	ORT Score: 8+
• No past or current substance use disorders • No family history of substance use disorders • No major or untreated psychopathology	• May be a history of substance use disorders • May be family history of problematic drug use • May have past or concurrent psychopathology • Not actively addicted	• Active substance use disorders • Major, untreated psychopathology • Actively addicted

Adapted from Gourlay 2005[17] and Webster 2005.[14]
ORT = Opioid Risk Tool. (See Figure 4.)

- Patients with 4 or more aberrant behaviors or positive results of a urine drug screen (random testing) may also be considered to be at moderate risk[12, 13]
- Patients with positive results of a urine drug screen from non-random screening may be considered high risk[12, 13]

Figure 4: Opioid Risk Tool (ORT)[14]

Risk stratification is also useful for guiding the approach to monitoring.

- In patients at low risk for adverse outcomes who receive stable doses of opioids, monitoring once every 3 to 6 months may be sufficient[2]
- Patients who may need more frequent or intense monitoring include older patients or those with a history of an addictive disorder, an occupation demanding mental acuity, an unstable or dysfunctional social environment, or comorbid psychiatric or medical conditions[2]
- In patients at very high risk, monitoring on a weekly basis may be necessary[2]

Guideline Spotlight

- HCPs may consider opioid therapy for patients with chronic noncancer pain and history of drug abuse, psychiatric issues, or serious aberrant drug-related behaviors only if they are able to implement more frequent and stringent monitoring parameters[2]

Treatment Plan and Agreement

HCPs should inform patients about the risks and benefits associated with treatment and gain their consent before initiating a trial of opioid therapy.[2, 18] Before prescribing opioid therapy, establish a treatment plan and an opioid use agreement.[1,2,18]

The treatment agreement can enhance the patient-HCP relationship and provides an opportunity for patient education and counseling. Treatment agreements can engage patients by making them active participants in their care, clarify roles, motivate adherence, avoid misunderstandings, and establish a foundation for future decision making.[1]

- Establish and document a treatment plan that includes goals of therapy, how opioids will be prescribed and taken, and expectations for follow-up and monitoring[2]
- Discuss the risks of and alternatives to opioid analgesics[2]
- For opioid analgesics with a Medication Guide, provide the Medication Guide to patients every time the medication is dispensed, as it may contain important new information[2,4,7,16]
- Document the treatment plan, including patient and HCP responsibilities and expectations for the appropriate and safe use of opioids, in an opioid use agreement[2]
- Psychotherapeutic interventions including cognitive-behavioral therapy should routinely be integrated into the pain management plan[2]

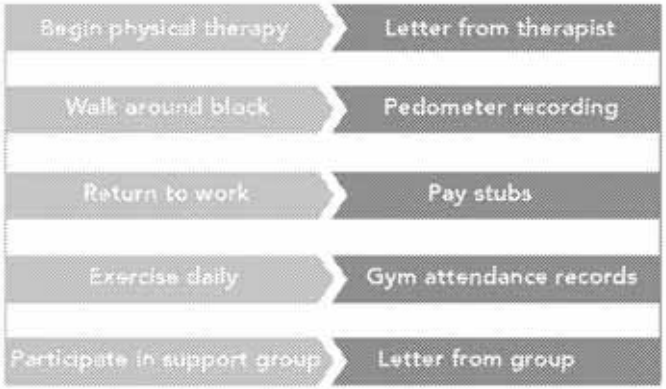
Guideline Spotlight

- When starting chronic opioid therapy, informed consent should be obtained. A continuing discussion with the patient regarding treatment should include goals, expectations, potential risks, and alternatives to opioid therapy[2]
- HCPs may consider using a written management plan to document patient and clinician responsibilities and expectations and assist in patient education[2]

Function-Based Treatment Goals

Because it is difficult to completely relieve pain, HCPs may consider shifting from focusing on analgesia to focusing on improved functioning (eg, getting out of bed, going back to work part time, attending more events outside the home).[1] Function-based therapy can increase patients' quality of life and reduce their burden of pain. Function-based treatment goals should be collaborative, realistic, achievable, meaningful to the patient, and verifiable.[1] See Figure 5 for examples of verifiable functional goals.[1]

Figure 5: Examples of Verifiable Functional Goals[1]



Initiating Opioid Therapy

Initiation of opioid therapy should be viewed as a short-term trial with a duration of several weeks to several months to determine appropriateness.[2]

Individual Treatment

Selection of the opioid to be prescribed, initial dosing, and titration should be individualized based on each patient's

- Health status[2]
- Prior opioid exposure[2]*
- Attainment of therapeutic goals[2]
- Predicted or observed harms[2]

*Many opioid analgesics, and high doses of most opioid analgesics, should be prescribed only for patients who are already opioid tolerant.[4, 6, 7, 16]

In the Selection of the Initial Opioid Dose, Give Attention to the Following[2, 4, 5, 6, 7, 16, 18, 20]:

- The type and severity of the patient's pain
- The daily dose, potency, and specific characteristics of the opioid the patient has been taking previously
- The reliability of the relative potency estimate used to calculate the equivalent opioid dose needed
- The patient's risk factors for overdose, including:
  - The patient's degree of opioid tolerance
  - The patient's age, general condition, and medical status
  - Concurrent use of nonopioid analgesics and other medications, such as those with CNS activity
- The patient's risk factors for misuse, abuse, addiction, or diversion, including a prior history of abuse, addiction, or diversion
- The balance between the risks and benefits

Special Cautions for Methadone Conversion, Initiation, and Titration

A number of epidemiologic studies suggest an increased rate of methadone – associated deaths in the United States[21, 22, 23]

Methadone is characterized by complicated and variable pharmacokinetics and pharmacodynamics and should be initiated and titrated cautiously, by clinicians familiar with its use and risks[2]

- Because of its very long and variable half-life, methadone must be titrated carefully to avoid the potential for delayed adverse events such as overdose[2]
- Although the half-life of methadone is usually estimated at 15-60 hours, a half-life as high as 120 hours has been reported[2]
- In a patient for whom the methadone half-life is 60 hours, it would take almost 12 days on a stable dose of methadone to approach a steady state[2]
- The ratio between methadone and other opioid agonists may vary widely as a function of previous dose exposure[7]
- Deaths, cardiac and respiratory, have been reported during initiation and conversion of pain patients to methadone treatment from treatment with other opioid agonists[24]
- Patients tolerant to other opioids may be incompletely tolerant to methadone[24]
- Deaths have occured in opioid tolerant patients during conversion to methadone[24]
- Methadone should be started at low doses and titrated slowly and increases should occur no more frequently than weekly[2]
- Particular vigilance is necessary during treatment initiation, conversion from an opioid to methadone, and during titration[2]
- It is extremely important to monitor all patients closely when converting from methadone to other opioid agonists[7]
- Methadone should not be used to treat breakthrough pain[2]

Find the Equianalgesic Dose

A recent Ad Hoc Expert Panel on Evidence Review and Guidelines for Opioid Rotation recommends utilization of existing equianalgesic dose tables when converting a dose from a patient's existing opioid therapy.[20]

These equianalgesic dose tables can be found in the prescribing information for each product (see Fine et al[20] for an evidence-based review of the current equianalgesic dose tables). Because of several limitations of these conversion ratios, the panel also recommended additional dose adjustments after calculation of the equianalgesic dose to determine the approximate starting dose.[20]

Determine the Approximate Starting Dose

To reduce the risk of unintended overdose, adjust the calculated conversion ratio based on a clinical assessment of risk.[20]

- Calculate an automatic safety factor
  - 25%–50% reduction in the equianalgesic dose for most oral opioids
  - 75%–90% reduction in the equianalgesic dose for patients switching to methadone
  - Adjustment not required when converting from oral or parenteral opioids to transdermal fentanyl
  - Initiate at the lowest available dose regardless of previous opioid regimen when converting to oral transmucosal fentanyl citrate
- Calculate an additional dose adjustment based on assessment of patient characteristics, including:
  - Pain severity at the time of conversion
  - Existence of other medical or psychosocial factors that potentially alter potency or the likelihood that the initial dose will be analgesic, relatively free of adverse effects, and unlikely to precipitate withdrawal
- HCPs should refer to the product labeling for additional information concerning risks and safe use

Titrate Opioid Therapy

It is important to titrate therapy for each patient individually for optimal analgesia with minimal adverse effects. HCPs should have a strategy to frequently assess the patient's initial response to opioid treatment and titrate to optimize outcomes[20]—that is, to the dose that provides adequate pain relief with tolerable adverse effects. Titration should take into account the time required for the new opioid to reach steady state, which may range from 24–36 hours to 6 days (Table 1).[4, 5, 6, 7, 16]

- Titrate to adequate pain relief with tolerable adverse effects
- Consider dose increases of 25%–50%
- Titrate no more frequently than it takes to reach steady state
- Assess pain relief and adverse reactions frequently
- Manage breakthrough pain and adverse reactions, such as constipation
- Consider dose increase if more than 2 medications per day for 2 consecutive days are needed for breakthrough pain

Table 1: Time to Steady State of Select Long-Acting Opioids[4, 5, 6, 7, 16]

Opioid Analgesic	Time to Steady State
OxyCodone ER	1–1.5 days
Morphine and naltrexone ER	2+ days*
Oxymorphone ER	3 days
Hydromorphone ER	3–4 days
Methadone	3–12+ days**
Fentanyl transdermal system	6 days

*Dose-related.
**See Special Cautions for Methadone, p. 18.

Patient Counseling

Before initiating treatment with opioid analgesics, counsel patients and caregivers on opioid risks and safe use.[2,4,7] Instruct patients to read the Medication Guide each time their opioid analgesic is dispensed because new information may be available.[2, 4, 7, 16] Topics to discuss with patients before initiating opioid therapy include:

- **Risks**
  - Potential for common opioid-related adverse effects, such as constipation, nausea, and sedation[2]
  - Potential for serious risks, including misuse, abuse, addiction, and overdose[2]
  - Potential risk of fatal overdose to anyone for whom it was not prescribed (especially children)
- **Safe Use Recommendations**
  - Certain opioids and high doses of most opioids are only for patients who are already receiving opioid pain medicine and whose bodies are used to taking these medications[4, 6, 7, 16]
  - Opioid analgesics must be taken only as directed[4, 6, 7]
  - Oral tablets designed to be swallowed whole should never be broken, chewed, dissolved, or crushed; the ingredients should not by snorted, injected, or inhaled; and transdermal opioids should not be taken orally, as doing so may result in a fatal overdose[4, 5, 6, 7, 16]
  - The opioid dose should not be changed without first consulting an HCP[2, 4, 7, 20]
  - Opioids should not be taken with alcohol or other medications that cause CNS or respiratory depression
- **Safe Handling Recommendations**
  - Opioid analgesics should be kept in a secure place out of the reach of anyone for whom they are not prescribed, especially children[2, 4, 6, 7]
  - Opioid analgesics should only be taken by the individuals for whom and for the conditions for which they have been prescribed[4, 6, 7]
  - Opioid analgesics are subject to misuse, abuse, addiction, overdose, and diversion, and should therefore be carefully stored to prevent theft[4, 6, 18]
  - It is against the law to sell or give away opioid medication[6, 15]
  - 70% of individuals aged 12 years and older who abuse prescription opioids obtain them from a friend or relative[11]

Guideline Spotlight

- HCPs should counsel women of childbearing potential about the risks and benefits of chronic opioid therapy during pregnancy and after delivery, and should encourage no use of chronic opioids during pregnancy unless the potential benefits outweigh risks[2]
- HCPs should counsel patients receiving chronic opioid therapy about transient or lasting cognitive impairment that may affect driving and work safety[2]

Periodic Patient Evaluation/Monitoring

During chronic opioid therapy, patients should be periodically re-evaluated to confirm the continued need for around-the-clock opioid therapy, as well as the appropriateness of current therapy based on pain control and adverse events.[2,4,5,6,7,16,18,20] Patients should also continue to be monitored for clinical risk of opioid abuse, addiction, or diversion, particularly with high-dose formulations.[7] Periodic reviews, like opioid treatment itself, should be individualized for each patient and guided by the HCP's own judgment.[1]

Clinicians should routinely carry out a thorough clinical assessment for presence of aberrant drug-related behaviors, substance use, and psychological issues. One tool (Figure 6) to aid in monitoring patients during the course of opioid therapy includes the 4As of outcome assessment.

- Analgesia (sustained efficacy)
  Pain must be monitored and documented at baseline and at all subsequent office visits using a validated scale for rating pain intensity.[25]
- Activities of daily living (functional status)
  Progress toward achieving therapeutic goals, including improvement in activities of daily living and psychosocial functioning, should be documented at each office visit.[25]
- Adverse effects*
  Optimal pain relief with minimal adverse effects is the goal of pain management. HCPs should monitor and manage opioid-associated adverse effects throughout treatment.[25]
- Aberrant drug-related behaviors
  Aberrant behaviors indicative of misuse, abuse, and addiction may arise in patients receiving long-term opioid therapy, and should therefore be assessed at every office visit and addressed if present.[25]

*Adverse event information may be reported to the FDA MedWatch Reporting System by phone at 1-800-FDA-1088 (1-800-332-1088) or by mail using Form 3500 at www.fda.gov/medwatch.

Behaviors Suggestive of Addiction, Include[15]:

- Inability to take medications on schedule
- Taking multiple doses at once
- Frequent reports of lost or stolen prescriptions
- Doctor shopping
- Isolation from family and friends
- Concomitant use of nonprescribed psychoactive drugs
- Use of analgesic medications for nonanalgesic effects
- Noncompliance to other treatments or evaluations
- Insistence on rapid-onset formulations or routes of administration
- Reports of no pain relief whatsoever with nonopioid analgesics

Figure 6: Pain Assessment and Documentation Tool (PADT)[26]

In addition to patient self-report, other monitoring tools to verify adherence to the therapeutic plan include:

- Urine drug screening (UDS)
  Routine UDS of all patients receiving opioid therapy can effectively detect the presence of nonprescribed or illicit substances or the lack of prescribed substances that would not be revealed by patient self-reporting alone.[2]
- Pill counts
  Pill or tablet counts can be used to verify adherence to the prescribed dosing regimen[2]
- Family member or caregiver interviews[2]
- Prescription monitoring program data[2]

Guideline Spotlight

- Clinicians should periodically obtain urine drug screens from all patients to confirm adherence to the opioid treatment plan, regardless of whether a patient is at high risk for, or has engaged in, aberrant drug-related behaviors[2]

Continuing Opioid Therapy

The decision to continue opioid therapy after the initial trial should be based on several key outcomes.[2]

- Progress in meeting defined therapeutic goals
- Presence and severity of adverse effects
- Change in underlying pain condition
- Change in psychiatric or medical comorbidities
- Identification of aberrant drug-related behavior, addiction, or diversion

Consultation and Referral

Patients with chronic noncancer pain have more comorbidities and are in greater need of health care services than other patients.[2] This complexity can present a clinical challenge for HCPs, who may find that some of their patients' needs fall outside their area of expertise.[1] When such circumstances arise, HCPs should refer patients to clinicians who possess the specialized skills required.[1,18] HCPs should coordinate patient consultation with, and facilitate communication between, these other health care professionals as needed.[2]

Guideline Spotlight

- HCPs should evaluate patients engaging in aberrant drug-related behaviors for appropriateness of opioid therapy or need for restructuring of therapy, referral for assistance in management, or discontinuation of opioid therapy[2]
- HCPs should pursue consultation, including interdisciplinary pain management, when patients with chronic noncancer pain may benefit from additional skills or resources they cannot provide[2]

Tips for Facilitating the Referral Process

- Do not delay in referring patients[1]
- Provide the information the consultant will need to evaluate the patient[1]
- Make the referral as specific as possible by explaining just how the consultant can help you and your patient[1]
- Maintain a current list of colleagues who may serve as consultants when the need arises[1]
- Have a "go-to" pain specialist and addiction specialist to whom you can refer patients at the ready[1]
- Communicate with consultants so you know what they're doing to help your patient[1]

Patients at High Risk

Patients who have a history of drug abuse and patients who are at high risk for aberrant drug-related behaviors do experience chronic noncancer pain, and these patients are entitled to effective pain management.[2, 17, 18] It is recognized, however, that prescribing opioids to patients who are at high risk poses a clinical challenge.[2]

Tips to help balance the risk-benefit profile in such patients include the following[1, 2]:

- More frequent and intense monitoring
- Authorization of limited prescription quantities
- Consultation or co-treatment with specialists in addiction medicine and / or mental health
- Re-evaluation and possible restructuring of therapy
- Temporary or permanent tapering of opioid doses
- Addition of psychological therapy or other nonopioid treatment
- Structured opioid agonist therapy with methadone or buprenorphine
- Possible referral for opioid detoxification and withdrawal management
- Discontinuation of treatment in patients known to be diverting opioids or engaging in seriously aberrant behaviors (eg, injecting oral formulations)

Guideline Spotlight

- When repeated dose escalations occur, HCPs should evaluate potential causes and reassess benefits relative to harms[2]
- In patients who require relatively high doses of chronic opioid therapy, HCPs should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the opioid use agreement on an ongoing basis, and consider more frequent follow-up visits[2]
- HCPs should taper or wean patients off chronic opioid therapy if they engage in repeated aberrant drug-related behaviors or drug abuse/diversion, experience no progress toward meeting therapeutic goals, or experience intolerable adverse effects[2]

Opioid Rotation

Opioid rotation, or a switch in the existing opioid therapy, involves changing an opioid analgesic or route of administration with the goal of improving patient outcomes.[20] Given the individual differences in patient response to different opioids, opioid rotation is a common clinical practice (Figure 7).[27]

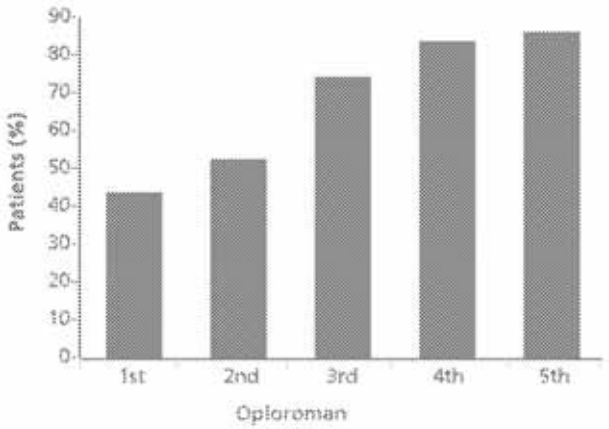
Indications for opioid rotation include:[20]

- Occurrence of intolerable adverse effects
- Poor analgesic efficacy despite aggressive dose titration
- Problematic drug-drug interactions
- Preference or need for a different route of administration
- Change in clinical status (eg, concern about drug abuse) or clinical setting that suggests benefit from another opioid
- Financial or drug-availability considerations

Guideline Spotlight

- HCPs should consider opioid rotation when patients experience intolerable adverse effects or inadequate benefit despite dose increases[2]

Figure 7: Percentage of Patients Requiring Different Opioids to Achieve an Optimal Response[28]



Exit Strategy

Termination of opioid therapy, rather than opioid rotation, should be considered under certain circumstances. When a patient is involved in illegal activity, such as selling prescriptions or forging signatures to obtain prescriptions, that patient should be terminated immediately. Termination should also be considered for patients with opioid addiction who refuse treatment for their addiction.[1] Some states may have specific legal or regulatory requirements for termination.

When terminating a patient from opioid therapy

- Meet with the patient and caregiver / family member to review the exit criteria in the treatment agreement and inform them of the reason for termination
- Clarify that termination is for the patient's benefit
- Clarify that pain management is not being abandoned
- Provide a list of names of other HCPs in the area or tell the patient to contact the local medical society to aid them in obtaining a list of HCPs
- Explain the effect of temporarily heightened pain to the patient
- Implement nonopioid pain strategies, such as psychiatric or behavioral therapy, physical therapy, nonopioid analgesics, treatment for insomnia, anxiety, or depression, and interventional procedures
- Refer patients with apparent addiction for addiction management
- Counsel patients on proper medication disposal
- Refer to each product's full Prescribing Information and Medication Guide for guidance

Discontinuation

In general, treatment with opioid analgesics should not be abruptly discontinued.[4,5,6,7,16] Safe discontinuation of opioid therapy requires gradual tapering of the opioid dose to prevent signs and symptoms of withdrawal in physically dependent patients.[1]

Documentation

The Federation of State Medical Boards expects HCPs to incorporate safeguards to minimize the potential for misuse, abuse, and diversion into their practices.[18] All opioid prescribing should be based on clear documentation of unrelieved pain.[18]

Records should be kept current and accessible at all times, and should include[1, 18]:

- More frequent and intense monitoring
- Results of diagnostic, therapeutic, and laboratory tests
- Evaluations and consultations
- Treatment objectives and goals
- Discussion of treatment risks and benefits
- Treatments
- Medications (including date, type, dosage, and quantity prescribed)
- Instructions and agreements
- Periodic reviews

Tools that can aid in the documentation of opioid therapy include:

- Informed consent and opioid use agreements[1]
- The ORT, SOAPP, and SOAPP-R tools to assess the potential for opioid abuse[2]
- The CAGE screening tool for identifying the presence of abuse[2]
- Urine drug screening to monitor patient adherence to opioid therapy[2]
- The PADT to assess treatment progress[25]

These tools are available through **caresalliance.org**

Understanding Applicable Laws, Policies, and Guidelines

Policies and laws that guide the treatment of chronic pain and are designed to enhance pain management are frequently updated and, therefore, should be reviewed by HCPs regularly.[1] The goals of these laws, policies, and guidelines are to achieve a rational balance between a patient's right to effective pain management and society's need to be protected from drug abuse.[1] Information on applicable laws guiding opioid prescribing and use can be accessed via the Federation of State Medical Boards website (http://www.fsmb.org).[1, 18]

HCPs who prescribe opioids must also be familiar with the Federal Controlled Substances Act (CSA), which gives authority to HCPs to prescribe, dispense, and administer controlled substances for legitimate medical purposes in the course of professional medicine.[1] The CSA also seeks to prevent diversion of controlled substances by controlling manufacturing and distribution, requiring documentation, and defining penalties for violation.[1] In addition, many states have established prescription monitoring programs to further address the problems of opioid diversion and abuse.[1]

Guideline Spotlight

- HCPs should be aware of current federal and state laws, regulatory guidelines, and policy statements that govern the medical use of chronic opioid therapy for chronic noncancer pain[2]

Summary

Opioid analgesics are a vital component of an effective strategy for the management of chronic noncancer pain. However, opioid analgesics are not appropriate for all patients. Awareness of the potential for misuse, abuse, addiction, overdose, and diversion is a responsibility of the HCP and the patient. HCPs who prescribe opioid analgesics must balance the risks of opioid therapy with the potential therapeutic benefits of these agents, and be knowledgeable in assessing and managing the risks associated with opioid therapy. With such knowledge, and by consistently and routinely employing responsible opioid prescribing and management practices, HCPs can help to mitigate the risks and optimize the benefits of opioid analgesics to improve outcomes for their patients with chronic noncancer pain.

For additional information on responsible opioid prescribing and safe use, please consult the following complimentary C.A.R.E.S. Alliance resources:

- Urine Drug Screening Primer
- Urine Drug Screening Practical Guide for Clinicians (Reprint)
- Opioid Clinical Management Education Booklet and CD
- Universal Precautions in Pain Medicine (Reprint)
- Opioid Treatment Guidelines (Reprint)
- Validated Pain and Risk Assessment Tools, including:
  - Brief Pain Inventory (BPI)
  - Opioid Risk Tool (ORT)
  - Numeric Rating Scale (NRS)
  - Pain Assessment and Documentation Tool (PADT)
- Opioid Safe Use and Handling Guide for Patients
- The C.A.R.E.S. Alliance website (www.caresalliance.org)
- Responsible Opioid Prescribing, A Physician's Guide by Scott M. Fishman

Glossary of Terms

Aberrant drug-related behavior: A behavior outside the boundaries of the treatment plan, which should be established and agreed upon as early as possible in the doctor-patient relationship.[2]

Abuse: Any use of an illegal drug, or the intentional self-administration of a medication for a nonmedical purpose, such as altering one's state of consciousness (eg, getting high).[2]

Addiction: A primary, chronic, neurobiologic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include 1 or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.[3]

Chronic opioid therapy: Daily or nearly-daily use of opioids for at least 90 days, often indefinitely.[2]

Diversion: The intentional transfer of a controlled substance from legitimate distribution and dispensing channels.[2]

Doctor shopping: Visiting multiple doctors to obtain additional prescriptions.

Drug-seeking behavior: Tactics include emergency calls or visits near the end of office hours; refusal to undergo appropriate examination, testing, or referral; repeated claims of loss of prescriptions; tampering with prescriptions; and reluctance to provide prior medical records or contact information for other treating physician(s).

Misuse: Use of a medication for a medical purpose other than as directed or as indicated, whether willful or unintentional, and whether harm results or not.[2]

Overdose: Use of larger quantities of a medication than can be physically tolerated, resulting in serious, often harmful, and sometimes fatal toxic reactions, including central nervous system and respiratory depression. Overdose can be manifested by respiratory depression, extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes pulmonary edema, bradycardia, hypotension, and death.[4,5,6,7]

Physical dependence: A state of adaptation that is manifested by an opioid specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[1]

Pseudoaddiction: Drug-seeking behavior that appears similar to addiction but is due to a need for more medication to control pain rather than psychological dependence on a drug.

Tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of 1 or more opioid effects over time.[1]

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